Make of record the accompanying declaration of one of the inventors.

R E M A R K S

The claims have been amended as to form, so as to take care of the matters raised by the Examiner under 35 USC §112, second paragraph, and in other needed ways.

The declaration of one of the inventors is submitted herewith, which confirms the data shown in Figs. 1 and 2 of our drawings.

Reconsideration is accordingly respectfully requested, for the rejection of the claims as unpatentable over the combination of eight references proposed in the Official Action.

In a nutshell:

The present claims are patentable over the combination of references, because the action of the absorption promoter and vasodilator is synergetic. Together, they more than triple the action of the absorption promoter alone. Their combined effect is far more than the mere addition of their individual effects. Furthermore, the vasodilator alone has almost no effect in promoting absorption of a physiologically active peptide by transmucosal administration. Therefore, a person of ordinary skill in this art, seeking to promote absorption, would never look to a vasodilator for that purpose.

In greater detail:

The present invention relates to a preparation for transmucosal administration comprising a combination of bioactive peptide and two additives, i.e. a compound having vasodilating activity and an absorption promotor having promoting action for the physiologically active peptide (= bioactive peptide) on nasal mucosa or rectal mucosa.

As shown in Fig. 2 of the present application and also in the inventor's declaration, a compound per se having vasodilating activity (vasodilator per se) has no absorption promoting action via the mucosa.

Also as shown in Fig. 2, the referential example, and the attached declaration, the use alone of an absorption promotor has only a small improvement of absorption promoting activity, but this is not a satisfactory result.

As clearly shown, the present invention shows advantageously superior absorption activity via the mucosa, e.g. nasal mucosa, as a result of using a combination of a vasodilator and an absorption promotor, as compared with the use of a vasodilator or an absorption promotor alone.

The object of the present invention is to promote absorption through mucosa, i.e. nasal mucosa, rectal mucosa or oral mucosa, with improved absorbability.

A term transdermal, for example as shown in the cited references, is concerned with an absorption through the skin, not through the mucosa, and the mechanism of absorption is different.

MASIZ 5,645,854 discloses transdermal absorption and not the transmucosal absorption of the present invention.

MASIZ essentially requires, for absorption through the skin, counter irritants or a vasodilator such as menthol, methylsalicylate, oil of wintergreen, peppermint oil or capsisium, with menthol being preferred. (MASIZ: column 3, lines 28-30).

MASIZ essentially requires a counter-irritant for transdermal action. The said irritant is, as disclosed in MASIZ, counter-irritant, which develops inflammation intradermally and produces a vasodilating function.

Thus, MASIZ discloses and teaches vasodilating activity by inflammatory activity. It relates to an improvement in permeation through the skin caused by use of the irritant alone.

In the transdermal absorption, i.e. absorption from the surface of the skin, such an irritant inflammatory vasodilating agent may be used. However, in transmucosal absorption such as nasal absorption, an irritant inflammatory vasodilator cannot be used.

MASIZ never discloses transmucosal absorption of the present invention. MASIZ rather discloses a composition, of which the irritant having vasodilating action by the onset of intrasurface inflammatory is disclosed and cannot be used in the present invention.

The compound having vasodilating action of the present invention has no inflammatory action on the tissues

such as very sensitive mucosa. The object of the preparation of the present invention is not transdermal absorption.

An object of ROBERTS et al. 5,750,141 is to provide a method of topical and/or transdermal administration of a vaso-active agent in combination with a therapeutic agent which is an anti-inflammatory agent or an anesthetic.

The vaso-active agent includes vasodilators, vasoconstrictors, a precursor of a vasodilator or vasoconstrictor. (ROBERTS et al. column 5, lines 56-58).

The vasodilator is described as

> "Examples of suitable vasodilators include lidocaine, nitroglyercin and other organic nitrates, or glyceryl tinitrate, papaverine, nicotines and various prostaglandins (more correctly eicosanoides) and various calcium antagonists." (ROBERTS et al. column 8, lines 5-9)

The present invention, by contrast, provides transmucosal absorption of bioactive peptide. As shown in Fig. 2 of the present application and also in the inventor's declaration, the vasodilator used in the present invention per se has no absorption promoting action through the mucosa.

ROBERTS et al. disclose low molecular weight anti-inflammatory agents or anesthetics with generally transdermal administration of water insoluble compounds. Contrary to ROBERTS et al., the present invention provides transmucosal absorption of water-soluble bioactive peptides and differs in the inventive concept. Furthermore, vasodilators per se show no transmucosal absorption activity for bioactive peptides.

Consequently, ROBERTS et al. neither disclose nor teach the present invention.

ROBERTS et al. disclose transdermal absorption by use of a vasodilator alone. The present invention effects transmucosal absorption of bioactive peptide using a combination of two compounds, i.e. a vasodilator, the use of which alone has no activity to absorb bioactive peptide, and an absorption promoter, the use of which alone is already known to effect incomplete absorption of the bioactive peptide.

As a result, the bioactive peptide can be absorbed much more readily through the mucosa by using the combination of these two compounds as compared with use of a single compound. Consequently, the present invention shows a superior effect which is neither disclosed in nor obvious from the description of ROBERTS et al.

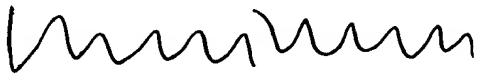
AZRIA et al. 5,149,537, KISSELL et al. ("Tolerability and Absorption Enhancement of Intranasally Administered Octreotide by Sodium Taurodihydrofusidate in Healthy Subjects", *Pharmaceutical Research*, Vol. 9, No. 1, 1992, pp. 52-57), etc. merely disclose improvements in absorption of drugs including bioactive peptide by the use of absorption promoters alone.

The present invention uses a combination of vasodilator and absorption promoter to effect excellent absorption of bioactive peptide via the mucosa. The effect of the present invention thus has never been disclosed by nor rendered obvious by the cited references.

As the claims as now constituted are believed to bring out these distinctions with ample particularity, it is believed that they are all patentable, and reconsideration and allowance are respectfully requested.

Respectfully submitted,

YOUNG & THOMPSON

By 

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